MAGNETIC NANOPARTICLES, MAGNETIC DETECTOR ARRAYS, AND METHODS FOR THEIR USE IN DETECTING BIOLOGICAL MOLECULES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Patent Application Ser. No. 60/519,378, filed Nov. 12, 2003, the contents of which are incorporated herein by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] The government may own rights in the present invention pursuant to grant number N00014-02-1-0807 from the U.S. Defense Advanced Research Projects Agency (DARPA).

FIELD OF THE INVENTION

[0003] The invention relates to magnetic nanoparticles, magnetic nanoparticle detectors, and methods of detecting biological materials, whether natural or synthetic, and whether modified or unmodified. The invention also relates to the magnetic nanoparticle materials for use in detecting biological materials, and methods for making those materials. Finally, the invention relates to magnetic particle detectors and related apparatus, as well as methods of using such apparatus for the detection of biological materials.

DESCRIPTION OF RELATED ART

[0004] The development of high sensitivity, quantitative DNA fragment detection and identification systems has been of growing importance in the fields of functional genomics, forensics, bio-defense, anti-bioterrorism, and other biotechnology applications.

[0005] Ideally, detection systems should be sensitive, rapid, portable, inexpensive, and reusable. Additionally, it is preferable that the systems do not require DNA amplification processes such as the polymerase chain reaction (PCR). More specifically, the system should preferably have the following characteristics: (1) one DNA fragment per tag, (2) each tag is individually detectable, (3) an effectively infinite number of detectors, and (4) known efficiency of the attachment processes involved. Currently, no system is commercially available that satisfies all of these requirements.

[0006] Numerous of the current microarray systems utilizing fluorescent labeling (tagging) are inherently of low sensitivity because they require approximately 104 molecules to achieve a useful signal to noise ratio (thereby violating the ability to have each tag be individually detectable) and are only marginally quantitative because of the optical systems involved, crosstalk, and bleaching (M. Schena, R. W. Davis, *Microarray Biochip Technology*, Eaton Publishing, pp. 1-18 (2000)). Further, the optical detection systems are usually used in conjunction with the polymerase chain reaction (PCR).

[0007] However, several groups have recently taken a new approach to detecting target molecules. In U.S. Pat. No. 5,981,297 to Baselt (issued Nov. 9, 1999), a group at the Naval Research laboratory offered both an apparatus and methods for detecting target molecules using a magnetoresistive or magnetostrictive magnetic field sensor having binding molecules attached which are reported to selectively bind target molecular species, which in turn are attached to paramagnetic polymer beads.

[0008] In a related published article by D. R. Baselt, et al., entitled "A Biosensor Based on Magnetoresistance Technology", (*Biosensors and Bioelectronics*, Vol. 13, no. 7-8: 731-739 (1998)), a magnetic detection system which they called BARC (Bead Array Counter) is offered. According to the article, the BARC measures the forces that bind molecules such as DNA together, and use these interactions to hold magnetic microbeads to a solid substrate. Microfabricated magnetoresistive transducers on the substrate are reported to indicate whether the beads are removed when pulled by magnetic forces, and can be adapted to chips for use in multi-analyte detection capabilities.

[0009] M. M. Miller, et al., ("A DNA Array Sensor Utilizing Magnetic Microbeads and Magnetoelectronic Detection", *Journal of Magnetism and Magnetic Materials,* 225: 138-144 (2001)) offers a multi-analyte biosensor that uses magnetic microbeads as labels to detect DNA hybridization on a micro-fabricated chip. The beads are detected using giant magnetoresistance magnetoelectronic sensors that are embedded in the chip itself, allowing for the simultaneous detection of eight different analytes.

[0010] In U.S. Patent Application 2002/0060565 (published May 23, 2002), Tondra suggests a ferromagnetic, thin-film based magnetic field detection system useful in detecting the presence of selected molecular species. According to the specification of this patent application, a magnetic field sensor is supported on a substrate that has a binding molecule layer positioned on a side of the substrate and is capable of selectively binding to the selected molecular species.

[0011] Finally, a group in Portugal has deployed spin valve sensors coupled with coils at proximity (D. L. Graham, et al., *J. Appl. Phys.,* 91: 7786 (2002)). The magnetic tags used were about 2 μm in diameter for the paramagnetic polystyrene balls, and similarly sized for the ferromagnetic particles. The larger tags were coupled to a much larger and not easily ascertainable number of DNA fragments, prejudicing the quantitative capabilities of the system. The dimensions of the tags and of the magnetic detector suggested in this paper limit the detector density to levels 10^2 to 10^4 less than the approach disclosed herein.

[0012] Despite the advances achieved so far, there still remains a need for detection systems which ideally meet all four desirable qualities listed above.

SUMMARY OF THE INVENTION

[0013] A system of magnetic nanoparticles and detector arrays are described. The system is useful for the high-sensitivity detection of nucleic acid molecules such as DNA. The nanoparticles can be high moment magnetic nanoparticles that are superparamagnetic, or antiferromagnetic nanoparticles which contain at least two layers of antiferromagnetically-coupled high moment ferromagnets.

DESCRIPTION OF THE FIGURES

[0014] The following figures form part of the present specification and are included to further demonstrate certain